ENDOMETRIOSIS—ITS SIGNIFICANCE*

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IN AUGUST, 1938, in an editorial,[3] attention was drawn to the fact that endometriosis was increasing in frequency and that there was probably some reason for it. It was felt that the increase might be due to delayed marriages and to lack of early and frequent child-bearing, and suggested that the economic difficulties of the day were responsible for the increased frequency.

Since that writing, all cases in my private practice have been very carefully explored, and any piece of tissue suggestive of endometriosis has been excised and fixed in Zenker's solution before the removal of any organ was begun. Probably, the fact that pieces of tissue have been separately removed and preserved, is partly responsible for the finding of increased numbers of this lesion. It is also probable that because of the great increase in total hysterectomies, with a wide exposure of the posterior cul-de-sac and the uterosacral ligaments, more small posterior lesions have been found. The high percentage of positive microscopic findings and the greater percentage of gross findings have led to the conclusion that endometriosis is brought about by a physiologic response to persistent and uninterrupted menstruation. Something (estrin?) stimulates the celomic epithelium and this stimulation causes the epithelium to attempt to produce small areas of endometrial tissue, endosalpingial tissue, or even endocervical tissue. So great is the concern about this lesion and its frequency, with its definite lowering of fertility, that patients with stigma of lowered fertility are urged to marry and bear children early. Normal girls over 23 are urged to have a child as soon as possible after marriage. Many men and women cannot afford to be burdened with children immediately after marriage; but as youth is the proper time to have children it is right that they be urged to do so. Dr. Thomas R. Goethals, of Boston, found that in 75 per cent of 200 private primiparae the average age at the birth of the first child was 28 years. All this fits into the theory that an apparent increase in this entity is due to the economic difficulties of our times. Sampson,[7] in 1924, reported 64 instances in 296 celiotomies, or 21.6 per cent, and, in 1925,[8] 98 out of 332, or 29.5 per cent—a total of 162 out of 628, or 25.7 per cent. These statistics of Doctor Sampson are high; but it must be remembered that at that time, because of his work with endometriosis, patients from everywhere, who were suspected of having the disease, were being sent to him. This, I believe, has something to do with the figures presented. The cases described in this article were sent because of varied pelvic pathology; and none were suspected of having endometriosis.

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Definition.—There are two main types of ectopic endometrium: In one, and this does not figure in this communication, the endometrium is found growing down from the endometrium into the myometrium. It may invade the myometrium very deeply, but usually is made up of a few glands growing away from the normal lining of the uterus; occasionally, the growth penetrates the entire uterus, and may even invade incidental fibroids that are present. This lesion is known as adenomyoma or adenomyosis.

The second type, and the one that is being discussed here, is made up of areas of ectopic endometrium, either in the ovary, tube, pelvic peritoneum, on the front of the uterus, or in the uterosacral ligament, *etc.* The lesion may be widespread and the whole pelvis bound down by adhesions, or there may be a spot no larger than the head of a pin. The area may be blue, black, or purple, or there may simply be a pucker in the otherwise smooth pelvic peritoneum. Sections of this tissue will show glands similar to endometrial glands and a stroma similar to endometrial stroma. This tissue may respond to the stimulation of estrin to produce the growth phase, or to progestin to produce the secretory phase, or to pregnancy to produce decidua in the stroma; but just as the basal layer of the normal endometrium does not react to any ovarian stimulus, so also this tumor may not. However, enough cases have been seen that respond to ovarian stimulation, and that are so very like endometrium in microscopic appearance, that it is fair to assume that they are one and the same thing. I doubt if anyone questions, now, that the endometrium of endometriosis is not similar to normal uterine endometrium.

Theories for Development.—Cullen,[1] long ago, showed that the first type of endometrioma, the adenomyoma, is a down-growth from the endometrium, and that the glands are often connected with the endometrium. In a series published[2] from the Massachusetts General Hospital, in 1934, it was definitely shown that this lesion was more frequently present in women who had had multiple pregnancies. This is due, perhaps, to the growth and involution of the uterus and the activity of the endometrium as it passes through numerous pregnancies. Perhaps small pieces of tissue are caught in the myometrium when the changes take place.

Sampson postulated the idea that endometriosis is due to two possibilities: One, that the endometrium during a normal menstrual period may be swept in a backward direction and flow into the peritoneal cavity and attach itself and grow upon or into any pelvic organ; two, that an ovarian endometrioma may menstruate, swell, and rupture, and in rupturing spread endometrium that is viable into the pelvis, or itself become attached to the peritoneum and grow and invade it. This study cannot refute this theory, nor does it attempt to do so. In nearly every one of our cases the tubes were patent—a proof that reflux could take place. All of us have seen reflux bleeding during a period. The many years of uninterrupted menstruation in these cases would seem to give greater chances for the endometrium to flow through and grow. If, however, the menstrual flow is due to sloughing off of tissue that has become anoxemic (a current theory of menstruation) I think that it is unlikely that the tissue

that comes through the tube would be viable. Nature certainly did not intend that reflux bleeding should be responsible for the growth of invasive tissue in the pelvis. Menstruation itself may be a kind of abnormality, for it occurs only infrequently in monkeys in their natural habitat.

The theory of lymphatic extension, that is metastasis of endometrium through the lymphatics, probably is not the correct method of its spread. However, many very able men believe in this theory.

Iwanoff and Meyer[4] have proposed that inasmuch as the plevic peritoneum is the celomic epithelium, and as the celomic epithelium is the original source of the endocervix, endosalpinx, and endometrium, this tissue may still contain groups of viable embryonic cells, and under certain conditions they may grow, and in growing reproduce what they produced in the embryo. It is thus possible that just as the endometrium and endosalpinx and endocervix respond to estrin and progestin by growth and function the pelvic peritoneum (celomic epithelium) may grow and produce if the stimulation is constant and not interrupted, as it should be, by pregnancy. Interruption of the menstrual cycle by pregnancy is a physiologic change in women. When it is realized that the frequency of endometriosis in patients with stigma of underdevelopment is twice as great as in those without it, this theory is even more tenable, for patients with underdevelopment may have more left-over cells. If pregnancy is a check upon the development of endometriosis, and I believe it is, what is there in pregnant women that checks the celomic epithelium from growing? Certainly estrin and progestin are produced in greater quantities during the pregnant than in the nonpregnant state. This normal physiologic process, although perhaps not preventing it, must have something to do with avoiding endometriosis. It is probable that this theory is the correct one, namely, that epithelium which originally grew endometrium can, under certain abnormal conditions, again produce cells capable of becoming endometrial tissue.

Symptoms, Diagnosis, and Treatment.—These have been described so many times that this paragraph will be brief. The symptom occuring most frequently is that of acquired dysmenorrhea, which is usually accompanied by a change (increase in the amount) of the menstrual flow. The physical diagnosis is not difficult in a patient over 29 years of age, who presents symptoms of pelvic inflammation, who has had no children, and who, on vaginal or rectal examination, has a moderately fixed pelvis, with a rough or shotty feeling in the posterior cul-de-sac. Such findings may be interpreted as the result of endometriosis. The treatment may be radical or conservative, depending upon the age of the patient, the extent of the disease, and the patient's desire for children. Occasionally, bilateral oophorectomy will be necessary. Roentgen therapy destroys ovarian function, and this is followed by atrophy of the endometriosis as well as atrophy of the normal endometrium. Therefore, one can be conservative when it is deemed best. In older women, radical surgery is best if it can be undertaken without danger to the life of the patient. This tumor can be very difficult to remove, and injury to the rectum, bladder, uterus, or intestines can occur. At operation, it is frequently noticed that the uterus is flexed backward upon itself, the fundus and cervix being

attached to one another, the uterosacral ligaments are obliterated, and the posterior cul-de-sac drawn up on back of the bent uterus. This must be recognized during operation, as perforations of the rectum or incomplete surgery may otherwise result. When the uterus is straightened out and the cul-de-sac freed, a very wide, raw area will be found on the posterior wall of the uterus and in the cul-de-sac of Douglas. This is definite evidence of abnormal development and endometriosis is often recovered from these areas. The uterosacral ligaments may be missing following release of the uterus and cul-de-sac.

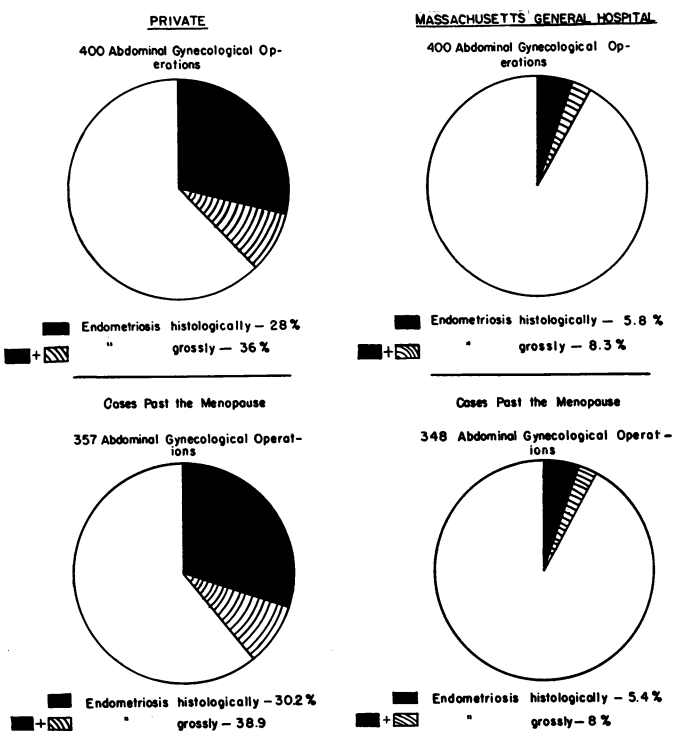
Increased Frequency.—The increased frequency may be actual, or it may be due to more careful observation and better exposure of the cul-de-sac and uterosacral ligaments. But there is probably more to it than that, for during my apprenticeship with the late Drs. W. P. Graves and G. W. W. Brewster, from 1921 to 1927, search was made for these lesions because of the great interest aroused by Doctor Sampson's observations. Yet not a great number of lesions were found. That is probably because the patients operated upon, then, were married earlier and bore children earlier than those who have been operated upon during the last four to five years. It is probably true that our mothers and grandmothers married early and had many children, and that they rarely had this abnormal physiologic process. There is no doubt that great interest stimulates more careful search. The habit of placing sutures about the areas, or placing safety-pins under them, or even excising the areas has been developed. In the early cases in this group, numerous areas of endometriosis were missed in the laboratory, for a blood-covered uterus is not the easiest place to find the fine, blue to purplish spots that represent this growth. Doctor Tracy B. Mallory, the Pathologist at the Massachusetts General Hospital, has admitted that my diagnosis, in the gross, is probably as correct as his by microscope; and if that is so, then the number is even greater than the histologic findings would indicate. I have been a student of this lesion since Doctor Sampson first drew attention to it, and I have worked and puzzled about it for years.

I believe that the theory of Iwanoff and Meyer is the correct one, and that the great frequency of endometriosis, as reported in this communication, is due to careful observation and the removal of pieces of tissue, but that the real reason for the frequency is that endometriomata are not tumors but represent abnormal physiology due to late marriage and delayed and infrequent child-bearing. The latter is due to the economic times we live in, and my plea is that patients with apparent infertility, evidences of underdevelopment, and older girls about to be married, be taught how to become pregnant and not how to avoid pregnancy, even though their finances are limited. The monkey mates as soon as she becomes of age, and has offspring until she can no longer have any or until she dies. Menstruation in this animal must be rare. As women have the same physiology it must be wrong to put off child-bearing until 14 to 20 years of menstrual life have passed. During a prolonged, uninterrupted menstrual career changes in the celomic epithelium from whence the endo-

metrium originally came must take place. Endometriomata are not true tumors but are areas of growth due to abnormal physiology. Another important finding is the comparison of private patients, most of them fairly well-to-do, to a similar group of patients at the Massachusetts General Hospital. The hospital patients are of that social status that marries early and has children frequently, and in this group there are fewer cases of endometriosis. Their more normal functions are reflected in the small incidence of endometriosis.

TABLE I

	Private	M. G. H.
Abdominal gynecologic operations	400	400
Histologic endometriosis	112–28%	23–5.8%
Gross endometriosis	144–36%	33–8.3%
Abdominal gynecologic operations		
Excluding cases past the menopause	357	348
Histologic endometriosis	108–30.2%	19–5.4%
Gross endometriosis	139–38.9%	28–8%



Diagrammatic representation of Table I.

The Material.—The last 400 consecutive abdominal gynecologic operations in my private practice were analyzed very carefully, and certain important findings noted. Four hundred consecutive patients who had had abdominal gynecologic operations at the Massachusetts General Hospital were studied to find the percentage of endometriosis to compare with the private group. In

the group of patients who came to my office, and were operated upon by me, 112, or 28 per cent, showed microscopic evidence of endometriosis, as against 5.8 per cent in the Massachusetts General Hospital group. The number of patients who were considered, grossly, to have endometriosis at operation was 144, or 36 per cent (Table I).

These patients were not, in many instances, suspected of having endometriosis before operation, and in many instances the endometrioma consisted of a very small isolated area. The point is, however, that they had what we understand as endometriosis, and it might easily have grown larger if let alone. The process was there, though not giving any symptoms.

A comparison was then made between the endometriosis group and the rest of the 400 who did not have endometriosis. In the endometriosis group, 74.1 per cent were married, and of the others, 74.3 per cent were married. In the endometriosis group, 53.1 per cent were over 25 when married, and in the other group, 57.3 per cent. These statistics are, so far, all nearly identical. But the fertility in the endometriosis group was 65.7 per cent, while in the other group it was 83.3 per cent (Table II). This latter figure for fertility is

TABLE II

400 ABDOMINAL GYNECOLOGIC OPERATIONS (PRIVATE)

	Endometriosis	No Endometriosis
Married	74.1%	74.3%
25 years of age or over at marriage	53.1%	57.3%
Two children or less	73.4%	49.3%
Fertility of married group	65.7%	83.3%
Stigma of underdevelopment	27.6%	15%
Marriage to first pregnancy over two years	69%	66.6%
Age at first pregnancy, 25 or over	63.4%	
Age at onset of symptoms, over 27 years	108 cases	
Menarche to endometriosis, 17 or more years	105 cases	
Number of years from menarche to first pregnancy 11 or more years	73%	
Age of patients with endometriosis over 29 years	All but one	

too low, but this is not unexpected, as most of the patients were operated upon for fibroids, cancer, bleeding, ovarian tumors, *etc.*, so that they also must have a lowered fertility. Reynolds and Macomber,[5] in their book on Fertility and Sterility, give 88 per cent as normal fertility in the married. Congenital erosions (exposure of the endocervix), very painful breasts, narrow pelvis, severe dysmenorrhea, juvenile uteri (measured), and infrequent periods were considered as stigma of underdevelopment. The endometriosis group had 27.6 per cent of patients with evidences of underdevelopment, while in the other group there were but 15 per cent. The endometriosis group, therefore, showed nearly twice as many patients with underdevelopment. Seventy-three and four-tenths per cent of the patients with endometriosis had two or less children, whereas in the other group 50.7 per cent had over two children. Sixty-nine per cent of the endometriosis group did not have the first child until two or more years after marriage, and of the other group 66.6 per cent did not. Other statistics of interest are as follows: For the group with endometriosis, the age at the first pregnancy was 25 or over in over 63.4 per cent; the age of the onset of symptoms was over 27 in 108 of 112 patients. The age of patients

with endometriosis, when it was found, was over 29, in all but one patient. The number of years from the onset of periods to the finding of endometriosis was 17 years or more in 105 out of 112 patients. In 57.4 per cent of the endometriosis group there was a change in the patient's characteristic menstrual flow. The preoperative diagnosis was made correctly in 41 per cent of patients. Endometriosis was found in the ovary in 57.1 per cent, on the peritoneal surface in 51.6 per cent, and in 18.7 per cent its location was the uterosacral ligament. In 32.1 per cent of patients dysmenorrhea was a complaint; 33 per cent complained of pain other than dysmenorrhea; 23 per cent had urinary difficulty; and 28.6 per cent had bowel habit changes. There were 85.7 per cent who had a radical operation, that is hysterectomy with or without removal of the ovaries, and but 14.3 per cent had conservative surgery. Three patients with conservative surgery had children following operation (Table III).

TABLE III

Region of Endiometriosis	
Ovary	57.1%
Peritoneum	51.6%
Uterosacral ligament	18.7%
Operation	
Radical	85.7%
Conservative	14.3%
Symptoms	
Dysmenorrhea	32.1%
Pain other than dysmenorrhea	33%
Urinary symptoms	23.2%
Change in catamenia	57.4%
Bowel symptoms	28.6%

CONCLUSIONS

(1) Delayed marriage, delayed and infrequent child-bearing all contribute to an increase noted in endometriosis.

(2) Less well-to-do patients in a general hospital population have less endometriosis than patients in private practice.

(3) Stigma of underdevelopment means lowered fertility and greater incidence of endometriosis.

(4) The celomic epithelium or pelvic peritoneum may be stimulated to produce endometriosis (Iwanoff and Meyer).

(5) Modern economic trends are responsible for delayed marriage.

(6) Young married couples should be urged to have children early, and practice contraception after they have their families. They should be taught how to have children, not to avoid them.

(7) Financial aid from parents in the early years of marriage should be offered and welcomed when possible.

The significance of endometriosis is that it is a stigma of infertility, and it is due to uninterrupted menstrual cycles, because of late marriage and infrequent child-bearing. Therefore, as it is increasing in private practice among those having children late in life and few in number, it is better for us, as doctors and fathers, to urge early marriage and early and frequent child-bearing.

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DISCUSSION.—DR. JAMES C. MASSON (Rochester, Minn.): Doctor Meigs' paper is on one of the subjects that are foremost in the minds of gynecologists at present, and there is no doubt that those who are "endometriosis-minded" find this condition frequently, whereas the general surgeons, and those who are not especially interested in the subject, see it rather rarely. I was impressed by the carefully prepared and convincing statistics of the essayist. There is no doubt that the condition is recognized more frequently than formerly, and the reason for this is probably that a real interest in the subject was stimulated by Sampson's paper about 20 years ago. Since that time, operations have become more frequent, especially more radical operations including total hysterectomy, and the more frequent examination of tissue removed has been, as suggested by Doctor Meigs, a factor in the more frequent recognition of the condition.

The possibility of delayed marriage, and of delayed child-bearing, has to be considered, but in this connection I would like to note that 50 per cent of the patients in my series were married before they were 24 years of age. I am sorry that I cannot give the dates when their first babies were born. In one case, endometriosis was diagnosed one year after the onset of the menstrual periods.

In one case, I reported to this Society in 1935, when I presented a paper on this subject, the patient had rather extensive endometriosis, in which the only serious lesion, I feel, was the one on the sigmoid. It was a benign tumor, but might grow sufficiently to cause obstruction. Another very important condition in this case was an adenomyoma in the rectovaginal septum. The "endometriosis-minded" surgeon frequently sees small implants in the cul-de-sac, on an ovary, or on the uterosacral ligaments. Many of them, I think, never cause serious trouble and, unless the tubes are occluded, pregnancy is still possible.

It is my impression that a great many of the smaller endometrial implants suggest, very strongly, Sampson's idea of a reversal of the flow of the menstrual fluid. I think a great many of them eventually disappear. I want you to keep in mind this picture, and I will refer later to large, tarry cysts and endometrial tumors in ectopic positions.

I want to draw attention to the number of cases in which endometriosis was located in the uterus in my series. In 482 of 576 cases encountered, the adenomyomata were in the uterus. A great many of these were diffuse adenomyosis of the uterus, but there were numerous implants on the visceral peritoneum. In 14 cases, endometrial implants were on the sigmoid, in 20 cases, in the rectovaginal septum, and in 77 cases, in the ovary. Some were huge, tarry cysts. In recent statistics, the number of large tumors or cysts remain about the same but there is a great increase in the smaller implants.

If persistent and uninterrupted menstrual periods have a marked influence on this condition, then I would think that a younger married woman would have to have many children to protect her until the time of her menopause. If she had two, three, or four children early, and then started contraceptive methods, she would have a long period of

constant and uninterrupted menstrual periods and, if Doctor Meigs' theory is correct, endometriosis might develop later in life.

Doctor Meigs has made a strong case for the hormonal influence of estrin on the columnar epithelium, as suggested by Meyer. In 1935, in speaking on this subject before this Society, I expressed the opinion that many of the tumors which are similar, microscopically, may have different origins, and I still believe it. Besides the stimulation of the columnar epithelium, I think the possibility of embryonic rests being stimulated in the same way and the occasional possibility of blood or lymph stream metastasis must be admitted. I have seen cases of endometriosis in the abdominal wall; and one case of endometriosis in the lung, and one instance of endometriosis in an arm have been reported. I think lesions of this type, which are microscopically similar to endometrium, could only reach such sites by way of the blood or lymph stream.

Doctor Sampson's theory seems reasonable and possible, especially in these multiple, small lesions which are scattered through the pelvis. I think it accounts for many of the ovarian implantations. It seems possible that the ovary is very susceptible, especially in an area where there is recent corpus luteum, and that an endometrial cell, becoming implanted there, will grow rapidly and produce tarry cysts. The tarry cyst ruptures and spreads endometrial tissue throughout the pelvis. Cullen's theory of direct extension is also possible in many cases.

I believe many smaller areas never grow, and probably are destroyed or absorbed by the peritoneum.

Doctor Meigs referred to underdevelopment. I have not paid attention to the etiologic factor he mentioned, as much as I should, but in cases of congenital anomalies of the pelvic organs, including absence of the uterus, with normal ovaries and normal internal secretion, I have not seen a case of endometriosis, in spite of the fact that some of these patients have been married several years.

Doctor Meigs has covered the diagnosis and symptoms, and there is no doubt that "endometriosis-minded" surgeons make a preoperative diagnosis in a large number of cases, and, at operation, suspected tissues are removed and examined more routinely by competent pathologists.

None of us, including Doctor Meigs, recognized many cases 20 years ago, but Doctor Sampson, in Albany, was finding endometriosis in more than 20 per cent of the cases in which he performed abdominal or pelvic operations as long ago as that. As Doctor Meigs suggested, it is possible he was seeing selected cases, but the incidence of endometriosis in his cases seems large compared to the incidence in most of our cases. Many of us, I am sure, do not remove or record many pin-head-size areas of discolored peritoneum when operating for some other major pathologic condition.

Among younger women, when it seems advisable to perform conservative operations, I believe it is advisable to cut the presacral nerve at the time of pelvic surgery, in order to relieve dysmenorrhea, which is often a major complaint.

No group of benign gynecologic conditions causes me more concern than advanced and extensive endometriosis among young women. In recent years, I have been more conservative than formerly, especially with the use of roentgen or radium irradiation. Now, I believe, the patient's best interests are being served by saving some ovarian tissue, in spite of the risk that a second operation may have to be performed or menopausal dose of radium or roentgen irradiation administered at a later date.

DR. JOE VINCENT MEIGS (Boston, Mass., closing): I would like to add just one or two things. Not all cysts with chocolate fluid in them are endometriomata. The diagnosis must be made histologically before it can be accepted, and a great many of these cysts are not true endometriomata.

If children are born when a patient is young, and there is, thereafter, a long uninterrupted series of periods, fibroids are likely to occur as well as other benign pelvic growths. I do not think there is any question about it.

The percentage of endometriosis will increase in relation to the number of small suspected areas that are removed before the surgery begins, and put in solution for the pathologist to examine.

The most important deduction from the paper is that, if 36 per cent of 400 patients have endometriosis, it must indicate that endometriomata are not true tumors at all. They must represent abnormal physiology.